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09/711,476	11/13/2000	C. Thomas Caskey	2875.1001-007	8353

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT PAPER NUMBER

1637

DATE MAILED: 03/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/711,476

Applicant(s)

CASKEY ET AL.

Examiner

Jeffrey Fredman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42 and 54-65 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 42 is/are allowed.
- 6) ☒ Claim(s) 54-64 is/are rejected.
- 7) ☒ Claim(s) 65 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Claim Interpretation***

1. The new amendment introduces the word "immobilized" into claim 54. The question is what does "immobilized" mean in this context? There are at least two different possible meanings. The first is that the primer may be immobilized indirectly by binding to the template, which is directly bound to a solid support. Under this interpretation, Soderlund remains anticipatory since Soderlund teaches that the primers are indirectly immobilized by interaction with a support bound template. A second, narrower interpretation, is that the primer itself is immobilized directly to the solid support without the template intermediate. The 103 rejection over Southern is based upon this interpretation.

### ***Claim Rejections - 35 USC § 102***

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 54-63 are rejected under 35 U.S.C. 102(b) and (e) as being anticipated by Soderlund (U.S. Patent 6,013,431) and Soderlund (WO 91/13075).

For ease of reference, the U.S. patent will be referred to for the rejection, but the Soderlund WO is identical in disclosure.

Soderlund teaches a method of analyzing a polynucleotide of interest for the presence or absence of an altered region (see abstract and preamble of claim 1, column 18) comprising the steps of:

a) annealing a single sample of the polynucleotide of interest to a plurality of primers (see column 9, lines 14-32, where a single sample is split into two tubes and annealed to two different primers (two being a plurality)), wherein the primers comprise an array of consecutive single stranded oligonucleotides having known sequences (see figure 3, primer 1 and primer 2) wherein each primer differs from the previous primer in the array by one base at the 3' end (see figure 3, primer 1 and primer 2) and wherein the primers are capable of hybridizing successively along the polynucleotide of interest, generating a plurality of annealed primers (see figure 3)

b) subjecting the primer complexes to a single base extension reaction using a polymerase to extend the annealed primers by the addition of a terminating nucleotide, generating a plurality of extended primers (see figure 3, where the terminator is ddY1, for example as well as column 8, lines 31-39 and columns 9-11),

c) observing the identity of each terminating nucleotide that has been added to each extended primer, thereby determining the identity of at least one nucleotide position of a polynucleotide of interest and thereby analyzing the polynucleotide of interest for the presence or absence of an altered region (see figure 3 and example 1, columns 9-11).

With regard to claim 55, Soderlund teaches the use of a polymerase and nucleotides corresponding to the four different bases (see column 8, lines 52-58).

With regard to claims 56-58, Soderlund teaches the use of multiple differentially labeled nucleotides (see column 8, lines 58-60 and column 19, claim 17).

Also, with regard to claim 58, Soderlund teaches the use of fluorescent-labels (see column 18, claim 8).

With regard to claim 59, Soderlund teaches analyzing either the coding or complementary non coding strands of a polynucleotide of interest (see abstract).

With regard to claim 60, Soderlund teaches the use of ddNTPs (see column 18, claim 6).

With regard to claims 61 and 62, Soderlund teaches primers between 14 and 40 bases (see column 6, lines 42-45) and exemplifies 20 mers (see column 9, line 66, primer D1, which is 20 nucleotides in length).

With regard to claim 63, Soderlund teaches primers of different lengths (see figure 3, primer 1 and primers 2 and 3 are of different lengths).

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 54-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Soderlund (U.S. Patent 6,013,431) or Soderlund (WO 91/13075), either in view of Mackay (U.S. Patent 4,874,492).

Soderlund teaches a method of analyzing a polynucleotide of interest for the presence or absence of an altered region (see abstract and preamble of claim 1, column 18) comprising the steps of:

a) annealing a single sample of the polynucleotide of interest to a plurality of primers (see column 9, lines 14-32, where a single sample is split into two tubes and annealed to two different primers (two being a plurality)), wherein the primers comprise an array of consecutive single stranded oligonucleotides having known sequences (see figure 3, primer 1 and primer 2) wherein each primer differs from the previous primer in the array by one base at the 3' end (see figure 3, primer 1 and primer 2) and wherein the primers are capable of hybridizing successively along the polynucleotide of interest, generating a plurality of annealed primers (see figure 3)

b) subjecting the primer complexes to a single base extension reaction using a polymerase to extend the annealed primers by the addition of a terminating nucleotide, generating a plurality of extended primers (see figure 3, where the terminator is ddY1, for example as well as column 8, lines 31-39 and columns 9-11),

c) observing the identity of each terminating nucleotide that has been added to each extended primer, thereby determining the identity of at least one nucleotide position of a polynucleotide of interest and thereby analyzing the polynucleotide of interest for the presence or absence of an altered region (see figure 3 and example 1, columns 9-11).

With regard to claim 55, Soderlund teaches the use of a polymerase and nucleotides corresponding to the four different bases (see column 8, lines 52-58).

With regard to claims 56-58, Soderlund teaches the use of multiple differentially labeled nucleotides (see column 8, lines 58-60 and column 19, claim 17).

Also, with regard to claim 58, Soderlund teaches the use of fluorescent labels (see column 18, claim 8).

With regard to claim 59, Soderlund teaches analyzing either the coding or complementary non coding strands of a polynucleotide of interest (see abstract).

With regard to claim 60, Soderlund teaches the use of ddNTPs (see column 18, claim 6).

With regard to claims 61 and 62, Soderlund teaches primers between 14 and 40 bases (see column 6, lines 42-45) and exemplifies 20 mers (see column 9, line 66, primer D1, which is 20 nucleotides in length).

With regard to claim 63, Soderlund teaches primers of different lengths (see figure 3, primer 1 and primers 2 and 3 are of different lengths).

Soderlund does not teach the use of a CCD device or of a photomultiplier for fluorescent detection.

Mackay teaches detection of nucleic acids with a CCD device (see abstract and columns 1 and 2)..

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the fluorescent detection method of Goelet in the method of Soderlund since Soderlund expressly teaches the use of fluorescent labels and Goelet teaches that such labels can be detected using CCD devices or photomultiplier tubes, stating "The invention enables analysis of the results of electrophoresis to be speeded up significantly as compared with autoradiography techniques, as well as increasing the accuracy obtainable and permitting use of smaller sample volumes than has been possible hitherto. The invention also greatly increases the range of integrated spot or band intensities contained within one array that can be handled, and allows much more accurate quantitation of the amount of say[sic] protein or DNA in each separated spot or band. (see column 4, lines 7-16)." So an ordinary practitioner would have been motivated to detect the fluorescent labels of Soderlund with the well known CCD device in order to improve accuracy, improve the range of intensities that can be detected and increase the speed while decreasing the amount of expensive reagents which are necessary.

7. Claims 54-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Soderlund (U.S. Patent 6,013,431) or Soderlund (WO 91/13075), either in view of Goelet et al (U.S. Patent 6,004,744).

Soderlund teaches a method of analyzing a polynucleotide of interest for the presence or absence of an altered region (see abstract and preamble of claim 1, column 18) comprising the steps of:

a) annealing a single sample of the polynucleotide of interest to a plurality of primers (see column 9, lines 14-32, where a single sample is split into two tubes and annealed to two different primers (two being a plurality)), wherein the primers comprise an array of consecutive single stranded oligonucleotides having known sequences (see figure 3, primer 1 and primer 2) wherein each primer differs from the previous primer in the array by one base at the 3' end (see figure 3, primer 1 and primer 2) and wherein the primers are capable of hybridizing successively along the polynucleotide of interest, generating a plurality of annealed primers (see figure 3)

b) subjecting the primer complexes to a single base extension reaction using a polymerase to extend the annealed primers by the addition of a terminating nucleotide, generating a plurality of extended primers (see figure 3, where the terminator is ddY1, for example as well as column 8, lines 31-39 and columns 9-11),

c) observing the identity of each terminating nucleotide that has been added to each extended primer, thereby determining the identity of at least one nucleotide position of a polynucleotide of interest and thereby analyzing the polynucleotide of

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interest for the presence or absence of an altered region (see figure 3 and example 1, columns 9-11).

With regard to claim 55, Soderlund teaches the use of a polymerase and nucleotides corresponding to the four different bases (see column 8, lines 52-58).

With regard to claims 56-58, Soderlund teaches the use of multiple differentially labeled nucleotides (see column 8, lines 58-60 and column 19, claim 17).

Also, with regard to claim 58, Soderlund teaches the use of fluorescent labels (see column 18, claim 8).

With regard to claim 59, Soderlund teaches analyzing either the coding or complementary non coding strands of a polynucleotide of interest (see abstract).

With regard to claim 60, Soderlund teaches the use of ddNTPs (see column 18, claim 6).

With regard to claims 61 and 62, Soderlund teaches primers between 14 and 40 bases (see column 6, lines 42-45) and exemplifies 20 mers (see column 9, line 66, primer D1, which is 20 nucleotides in length).

With regard to claim 63, Soderlund teaches primers of different lengths (see figure 3, primer 1 and primers 2 and 3 are of different lengths).

Soderlund does not teach direct immobilization of the primers to the solid support.

Goulet teaches a method of analyzing a polynucleotide of interest for the presence or absence of an altered region (see column 23, lines 43-51) where the primer is directly immobilized to the solid support (see column 23, lines 1-10), comprising the steps of:

(a) annealing a single sample of the polynucleotide of interest to a plurality of primers wherein the primers comprise an array of IMMOBILIZED single stranded oligonucleotides having known sequence (see column 23, lines 15-20),

(b) subjecting the plurality of annealed primers to a single base extension reaction to extend each annealed primer by addition of a terminating nucleotide to form a plurality of extended primers (see column 23, lines 20-26),

(c) observing the identity of each terminating nucleotide that has been added to each extended primer (see column 23, lines 30-42) thereby analyzing the polynucleotide of interest for the presence or absence of an altered region (see column 23, lines 43-51).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the array based methods of Goulet in the method of Soderlund since Soderlund teaches multiplex detection of the mutations (see example 5) and since Goelet expressly notes that "Specifically, the preferred embodiment, Genetic Bit Analysis (GBA), presents a more convenient solid phase. Magnetic microspheres must be manipulated with care in order to effectively wash and resuspend them. It is therefore difficult to envisage high volume, automated assays using these

beads. Furthermore, they are deeply colored and are not adapted to calorimetric or fluorescent assays. The GBA methodology has been adapted to allow the utilization of standard, polystyrene, 96-well microplates. These have the advantage of being widely used in clinical and research laboratories. There are a large number of liquid handling systems, including automated systems, adapted to this format. They are suited to optical signal detection methods and automated plate readers for different types of light detection are available (see column 25, line 38 to column 26, line 6)."

Goulet further expressly indicates that bound primer is preferable to bound template, directly suggesting the modification to Soderlund, when Goelet states "In the previously described method, the template was prepared by PCR using derivatized primers to permit immobilization of the template on the solid phase. Derivitization of the template is no longer necessary when the primer is immobilized. Rather, using unequal concentrations of PCR primers in an otherwise standard PCR, it is possible to generate an excess of one single-stranded molecule or the other, depending on which primer is in excess. These serve as convenient templates for hybridization to plate-bound GBA primer molecules (see column 26, lines 39-45)." Therefore the ordinary practitioner, here the scientist interested in analyzing point mutations, would recognize that a single modification of Soderlund to use primers attached to supports would be advantageous for the reasons given by Goulet, including the ability to perform high volume automated assays, fluorescent assays thereby avoiding radioactivity, and to avoid the need to derivatize the template. In this instance, each reference differs from the claimed

invention in only one step, and Goulet clearly suggests the elements missing from Soderlund.

### ***Allowable Subject Matter***

8. The following is a statement of reasons for the indication of allowable subject matter: Amended claim 42 is free of the prior art. The claim is drawn to an embodiment in which the oligonucleotide array is regenerated by digestion of the newly added nucleotide after completion of the assay. The cited prior art of Soderlund, Goulet, Rust, or Cantor in the IDS, do not teach regeneration of the array by cleavage mechanisms.

9. Claim 65 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. There is no teaching in Soderlund, Southern or Goelet to use dinucleotides, nor in any of the other cited prior art. Soderlund uses two nucleotides sequentially as in figure 3, but never a single dinucleotide molecule for termination.

### ***Response to Arguments***

10. Applicant's arguments filed December 20, 2004 have been fully considered but they are not persuasive.

Applicant argues that Soderlund teaches an immobilized template but that the primer is not immobilized. As noted in the claim interpretation section above, if the primer is annealed to an immobilized template, then it is, itself immobilized. So under this interpretation of the claim, Soderlund remains anticipatory. A new 103 rejection

over Goulet is added to address the situation of where the claim is interpreted such that the primer is directly immobilized to the solid support.

### ***Conclusion***

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jeffrey Fredman  
Primary Examiner  
Art Unit 1637

2/2/05